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Nuclear factor-kappa B links carcinogenic and chemopreventive agents

Ranju Ralhan, Manoj K. Pandey, Bharat B. Aggarwal

Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 143, Houston, TX 77030, USA

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1. ABSTRACT

Cancer prevention requires avoidance of tobacco, alcohol, high-fat diet, polluted air and water, sedentary lifestyle, and of mechanical, physical, psychological, or chemical stress. How these factors can cause cancer, is suggested by the transcription nuclear factor-kappa B (NF-κB), that is activated by tobacco, alcohol, high-fat diet, environment pollutants, cancer-causing viruses and bacteria (Helicobacter pylori), ultraviolet light, ionizing radiation, obesity, and stress. Furthermore, NF-κB–regulated gene products have been implicated in transformation of cells, and in proliferation, survival, invasion, angiogenesis, and metastasis. Suppression of NF-κB activation by the phytochemicals present in fruits and vegetables provides the molecular basis for their ability to prevent cancer. Other agents identified from spices and Ayurvedic and traditional Chinese medicines also been found to suppress NF-κB activation and thus may have potential for cancer prevention. The classic chemopreventive agent should offer long-term safety, low cost, and efficacy. The current review discuses in detail numerous agents such as curcumin, resveratrol, silymarin, catechins and others as potential chemopreventive agents. Thus, cancer, an ancient problem, may have an ancient solution.

2. INTRODUCTION

President Richard Nixon, in his 1971 State of the Union address, pledged "I will ask for an appropriation of an extra $100 million to launch an extensive campaign to find a cure to cancer. Let us make a total national commitment to conquer this dread disease. America has long been the wealthiest nation in the world. Now it is time we became the healthiest nation in the world." This appropriation led to creation of the National Cancer Institute (NCI). Since then over $200 billion has been spent, 1.56 million papers published, and 150,855 studies in mice reported (1). In spite of this, the U.S. cancer death rate was the same in 2002 as it was in 1950 (193.9 per 100,000 vs 193.4 per 100,000). It is time to rethink our approach to cancer.

Although we have learned a great deal about cancer biology within the last three decades, prevention and treatment of cancer are lagging. The discoveries of various oncogenes, tumor suppressor genes, tumor-specific genetic alterations, tumor cell growth factors and their receptors, cell signaling networks in tumor cells, protein kinases, and

epigenetic changes; recognition of the role of environmental factors in carcinogenesis; sequencing of the human genome; and advancements in the fields of genomics, proteomics, and glycomics are all major achievements in our understanding of what is cancer and what causes cancer; but the knowledge of how to prevent or treat the disease is still lacking. Research has suggested that, of the 30,000 genes that constitute man, as many as 400 are altered in all cancers. According to some estimates, as many as 300 different kinases are involved in cancer transformation and growth. Most cancers have an incubation period of 20 to 30 years before they are detectable; if the process of tumorigenesis starts at age 20 years, the cancer may not be detectable even by the best available method until age 40 or much later. The process of tumorgenesis may be reversible at early stages but becomes irreversible at later stages, and if not stopped will spread to other organs. Even if cancer-related genetic alterations are recognized, we do not fully understand how many such alterations are required before clinical symptoms of cancer appear. Some estimates indicate that as many as 30% of all cancers are indolent. Whether indolent cancers exhibit genetic changes similar to those of cancers with clinical symptoms is not clear.

3. CAUSES OF MAJOR CANCERS

The reason that cancer is easier to prevent than to treat is that effective treatment requires targeting of multiple pathways. Mono-targeted therapy has shown limited promise. Because we do not yet know which pathways are critical for cancer growth, the multi-targeted approach to therapy is in the early phase of development.

The road to prevention of cancer, however, appears to be more clear (2). Numerous lines of evidence have revealed that cancer is a disease of lifestyle. According to some estimates, as many as 80% of all cancers are preventable by change in lifestyle. Perhaps the foremost evidence for this comes from the epidemiology of cancer, which implicates lifestyle in the etiology of various types of cancers. Cancers of the lung, breast, colon, and prostate, for example, while the most common cancer types in the Western world, are among the least common types (10-100 fold less) in Asian countries, such as India, China, and Japan (3). Immigrants from Asian countries to the West experience these four cancers at rates similar to those of their adopted country, strongly suggesting that lifestyle, not genetic make-up, plays the dominant role in these cancers (4, 5).

Many other lines of evidence support the impact of lifestyle in causing cancer. Extensive research has revealed that certain types of cancers are maximally associated with cigarette smoking. For instance, as many as 90% of all lung cancer patients are cigarette smokers. Cigarette smoke has been linked with cancers of the lung, colon, pancreas, esophagus, thyroid, and head and neck (6). As many as one third of all cancers are linked with either cigarette smoke or smokeless tobacco (7). Alcohol is a major risk factor for certain cancers, including those of the esophagus, liver, and pancreas (8-10). A diet high in fat (such as red meat), obesity, and sedentary lifestyle have been linked with cancers of the colon, breast, and other sites (11, 12). Evidence now indicates that meat consumption increases the incidences of cancers of the stomach, colon and rectum, breast, and pancreas (13-20). Moreover, grilled and fried foods have been linked with certain types of cancer (21, 22).

Numerous additional lines of evidence suggest that the primary cause of most cancers is well understood. Environmental pollutants such as diesel fuel, lead, cadmium, arsenic, and petrochemicals all have been linked with various cancers (23-25). Evidence has emerged recently that different types of stress increase the incidence of certain types of cancers (26, 27). Finally, infection with certain viruses and bacteria can lead to cancer; examples include cervical cancer, liver cancer, stomach cancer, and certain lymphomas (28-30)

4. MECHANISM OF CARCINOGENESIS

How these various cancer risk factors actually cause cancer is fairly well understood. Like genetic mutations and epigenetic changes, transcription factors play an important role in tumorigenesis. Various transcription factors, including nuclear factor-kappa B (NF-κB), c-jun, AP-1, c-fos, peroxisome proliferator-activated receptor gamma (PPAR-γ), beta catenin, hypoxia-inducible factor 1 (HIF-1), SP-1, signal transducer activators of transcription (STATs), and nuclear factor-E2-related factor 2 (NRF2) have been linked to carcinogenic processes. Of all these factors, NF-κB is perhaps most closely linked to transformation, proliferation, invasion, angiogenesis, and metastasis of tumors (31).

5. INFLAMMATION AS A TARGET FOR CANCER PREVENTION

Inflammation was characterized by Cornelius Celsus, a physician in 1st century Rome, as heat, pain, redness, and swelling. In the 19th century, Rudolf Virchow from Würzburg, Germany, linked inflammation with atherosclerosis, rheumatoid arthritis, multiple sclerosis, asthma, Alzheimer's disease, and cancer, and coined the suffix "-itis." It appears that chronic inflammation over a long period of time can lead to cancer. For instance bronchitis, an inflammation of the bronchus, can lead to lung cancer; colitis, hepatitis, cystitis, esophagitis, and gastritis can lead to cancer of the colon, liver, bladder, esophagus, and stomach, respectively. It is also becoming apparent that most known cancer risk factors can cause inflammation. Tobacco smoke, grilled food, fried food, red meat, stress, diesel fuel, alcohol bile acid, ultraviolet light and infection with *Helicobacter pylori*, human papillomavirus, human hepatitis B virusor Epstein-Barr virus) all can result in inflammation (32-41).

Several biochemical markers of inflammation have been identified. These include cytokines such as tumor necrosis factor (TNF), interleukins (IL) -1, -6, -17, and -18, and chemokines; enzymes such as cyclo-oxygenase 2 (COX-2), 5-lipoxygenase (5-LOX), urokinase-type plasminogen activator (UPA), matrix metalloproteinase (MMP)-9, and inducible nitric oxide

Table 1. Chemopreventive agents under trial against cancers

Chemopreventive Agent	Types of Cancer
Celecoxib, rofecoxib, Nonsteroidal anti-inflammatory drugs (NSAIDs)	Colon, bladder, esophagus, lung, head and neck, breast, cervix, liver
Nitric oxide ("NO") donating (NO- NSAIDs)	Colon, prostate, bladder, head and neck
Zileuton, zafirkulast, licofelone	Lung, colon, esophagus
EP1 receptor antagonist (ONO-8711)	Breast, colon, head and neck
Bortezomib, R-flurbiprofen,	Prostate, colon, head and neck, multiple myeloma, liver
Curcumin, tea polyphenols, statins, Dithiolthiones, phenethyl isothiocyanate (PEITC)	Lung, liver, head and neck, prostate
Iloprost	Lung
Azacytidine, folic acid	Prostate, lung
Suberanilohydroxamic acid (SAHA)	Breast, colon
Finasteride, dutasteride	Prostate
Flutamide, bicalutamide, 3,3-diindoylmethane	Prostate
Exemestane, letrozole, anastrozole	Breast, prostate
Tamoxifen, toremifene, arzoxifene, raloxifene, soy isoflavones, acolfibene	Breast, prostate, colon
Indole-3-carbinol, 3,3-diindoylmethane Resveratrol, steroidal anti-estrogen (TAS-108)	Prostate, colon, breast, ovary
Rosiglitazone, pioglitazone, CDDO, Bexarotene (LGD100268)	Breast, colon, head and neck, liver
Fenretinide, 9-cis-retinoic acid	Breast, ovary, colon, head and neck
9-cis-retinoic acid	Breast, skin, head and neck
Targretin, Bexarotene (LGD100268)	Breast
Vitamin D3 analogues	Colon, prostate
Bcl-2 family inhibitor (ABT-737)	Colon, prostate
Exisulind	Prostate, colon
Gefitinib, erlotinib, Inhibitor of EGFR (EKB569)	Lung, bladder, breast, colon
Statins cetuximab	Colon, skin (melanoma), breast, prostate
Marimistat, prinomastat	Colon
Inhinbitors of Mammalian target of Rapamycin (mTOR)RAD-001	Prostate
Difluoromethylornithine (DFMO)	Colon, bladder, skin
Maleimide Analogs (CP31398)	Lung, esophagus, head and neck
Deguelin, Bexarotene (LGD100268)	Head and neck, lung
Tipifarnib, perillyl alcohol	Colon, pancreas, lung
Bevacizumab	Colon, breast

synthase (iNOS); adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), endothelial leukocyte adhesion molecule 1 (ELAM-1), and vascular cell adhesion molecule 1 (VCAM-1); and angiogenic factors such as vascular endothelial growth factor (VEGF), IL-8, and TNF. For more information about these factors, refer to our published review of the inflammatory network that is commonly encountered in cancer cells (42, 43). Interestingly, what all these markers of inflammation have in common is that they are regulated by NF-κB.

NF-κB was originally discovered by Baltimore *et al.* in activated B cells as having DNA-binding activity with affinity for the transcriptional enhancer of the immunoglobulin kappa light chain gene (44) and was correlated with the expression of antibody. However, B cells from NF-κB knockout mice have been found to have normal antibody production. In his recent review, Baltimore stated, "In fact, while the name NF-κB remains, none of the information it implies is fully correct. As mentioned, NF-κB is neither a critical regulator of the κ light-chain gene, nor is it B cell specific, nor truly a nuclear factor" (45).

This raises the question, what is NF-κB? Research over the last 20 years has revealed that NF-κB is a transcription factor that is present in every cell type and is conserved from *Drosophila* to man. Under resting conditions, it resides in the cytoplasm, but when activated, NF-κB translocates to the nucleus, binds DNA, and regulates the transcription of over 400 different gene products. These gene products in turn regulate inflammation, apoptosis, proliferation, invasion, angiogenesis, bone metabolism, atherosclerosis, and other processes. Hundreds of stimuli have been identified that can activate NF-κB; these include inflammatory cytokines, reactive oxygen intermediates, stress, environmental pollutants, cigarette smoke, hypoxia, heavy metals, acidic environments, alcohol, viruses, bacteria, endotoxin, tumor promoters, and growth factors (Figure 1).

Numerous lines of evidence suggest that NF-κB is a major mediator of carcinogenesis. NF-κB activation has been linked with transformation of cells. NF-κB–regulated gene products such as bcl-2, bcl-xl, inhibitor of apoptosis protein (IAP), X chromosome–linked IAP (XIAP), survivin, and Fas-associated death domain protein-like IL-1-β-converting enzyme inhibitory protein (cFLIP) have been shown to suppress apoptosis (Figure 2). NF-κB–regulated gene products such as c-myc, cyclin D1, and COX-2 have been shown to promote proliferation. NF-κB–regulated products such IL-6, TNF, IL-1, and chemokines are major mediators of inflammation. Inflammation recently has been linked with cancer, and this linkage again is mediated through NF-κB. Both COX-2 and 5-LOX, which have been linked with carcinogenesis, are regulated by NF-κB. The enzymes MMP-9 and UPA, linked with invasion, are regulated by NF-κB. VEGF, ICAM-1, ELAM-1, and VCAM-1, which mediate angiogenesis and metastasis, are regulated by NF-κB. Most agents that activate NF-κB are mediators of carcinogenesis. Most carcinogens that have been used to induce tumors in rodents or are linked to tumorigenesis in man activate NF-κB. Constitutive activation of NF-κB is observed

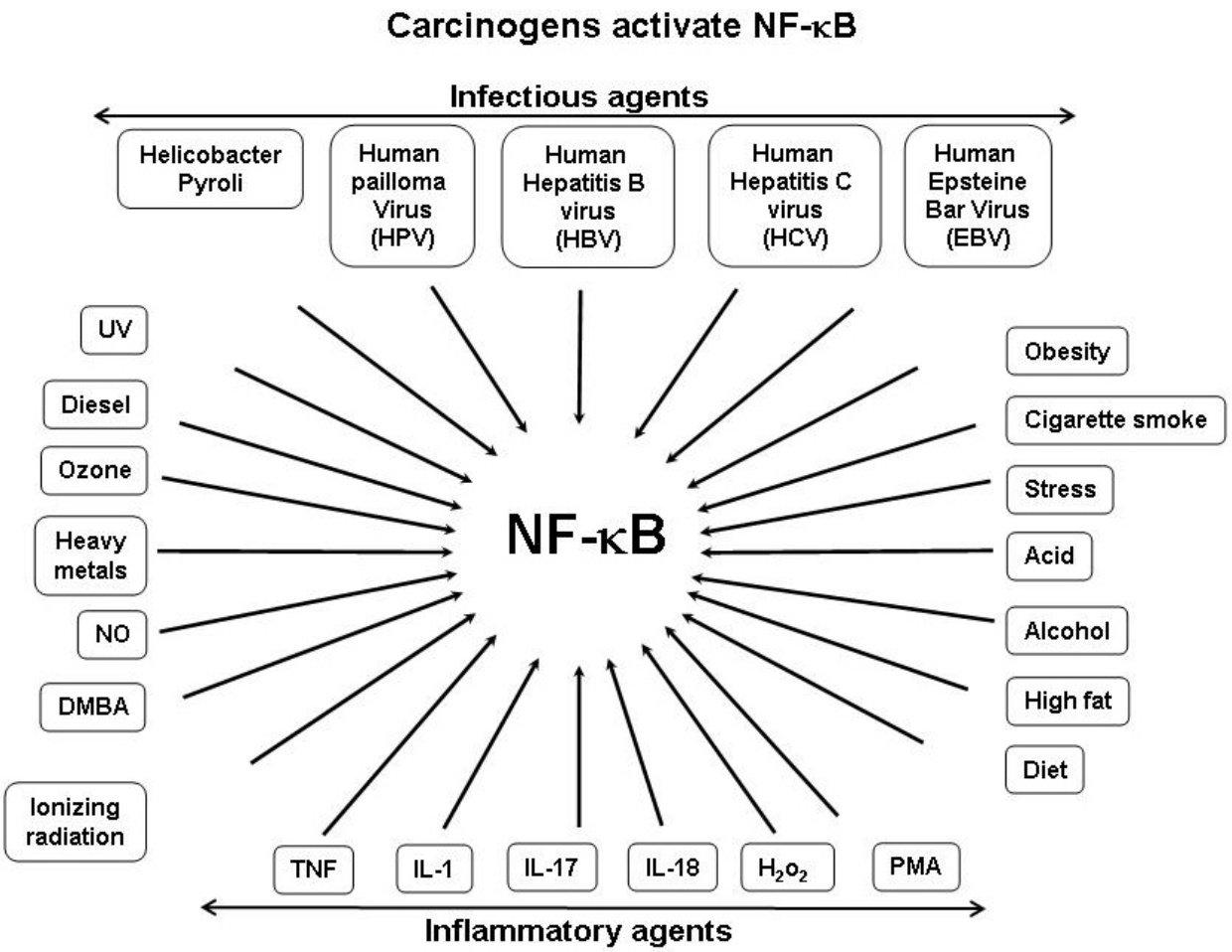

Figure 1. Carcinogens activate NF-κB.

frequently in tumor cells and not in normal cells. Evidence also has emerged that suppression of NF-κB activation may inhibit tumorigenesis. All these findings provide compelling evidence that NF-κB is likely a major mediator of tumorigenesis.

If NF-κB is a mediator of tumorigenesis, suppression of NF-κB should prevent cancer. Chemoprevention is a term first introduced almost three decades ago by Dr. Michael Sporn, then at the NCI, for prevention of chemical-induced carcinogenesis. Since any chemopreventive agent must be administered over a long period of time, it must be safe, it should be inexpensive, and it should be efficacious. Although retinoids, carotenoids, tocopherol (vitamin E), selenium, COX-2 inhibitors (celecoxib), and ornithine decarboxylase inhibitors have been tested for chemoprevention, none of them so far has shown any promise (Table 1), perhaps because of our limited knowledge of the mechanism of carcinogenesis. The latest paradigm for cancer prevention and treatment requires that the agent should have multiple targets rather than a single target, an acknowledgment of the complexity of carcinogenesis (46-48). Several agents identified from fruits, vegetables, spices, and traditional medicines have been shown to have chemopreventive activities in animals (Table 2). It appears that most natural agents inhibit multiple targets, perhaps part if not all of the reason that they are less toxic (Figure 3). The following section contains descriptions of some of the chemopreventive agents that meet these requirements and are inhibitors of NF-κB

5.1. Curcumin

Curcumin (diferuloylmethane) is an active component of turmeric (*Curcuma longa*), used as a spice and as an Ayurvedic medicine for centuries on the Indian subcontinent (47, 49). Curcumin has been shown to suppress carcinogenesis in the skin, liver, lung, colon, stomach, and breast. It also has been shown to inhibit the proliferation of a wide variety of tumor cells in culture and promote apoptosis through Bid cleavage, cytochrome C release, and activation of caspase-9 and caspase-3. Curcumin has been shown to lower blood cholesterol, promote wound healing, prevent skin wrinkling, inhibit inflammation, suppress rheumatoid arthritis, and inhibit human immunodeficiency virus replication. Curcumin mediates this wide variety of therapeutic effects through regulation of transcription factors NF-κB, AP-1, HIF-1,

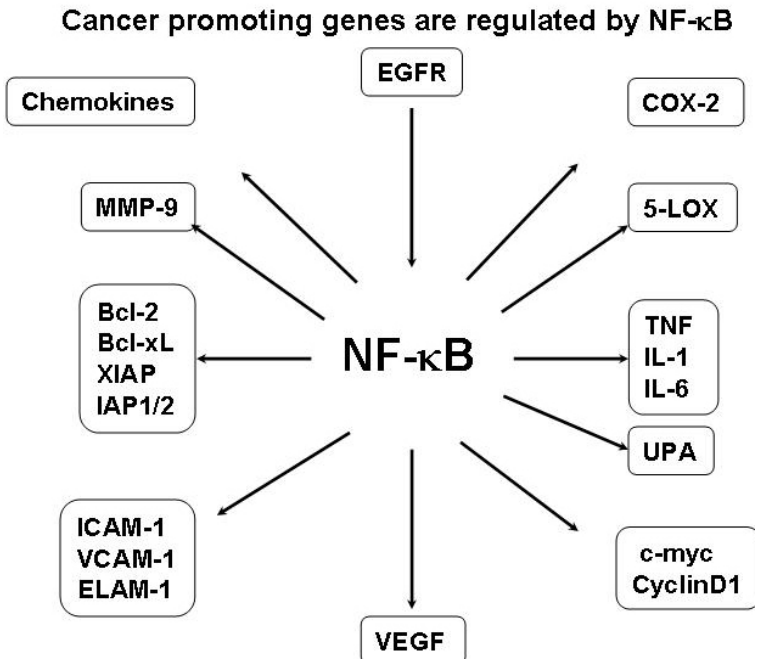

Figure 2. Cancer promoting genes are regulated by NF-κB.

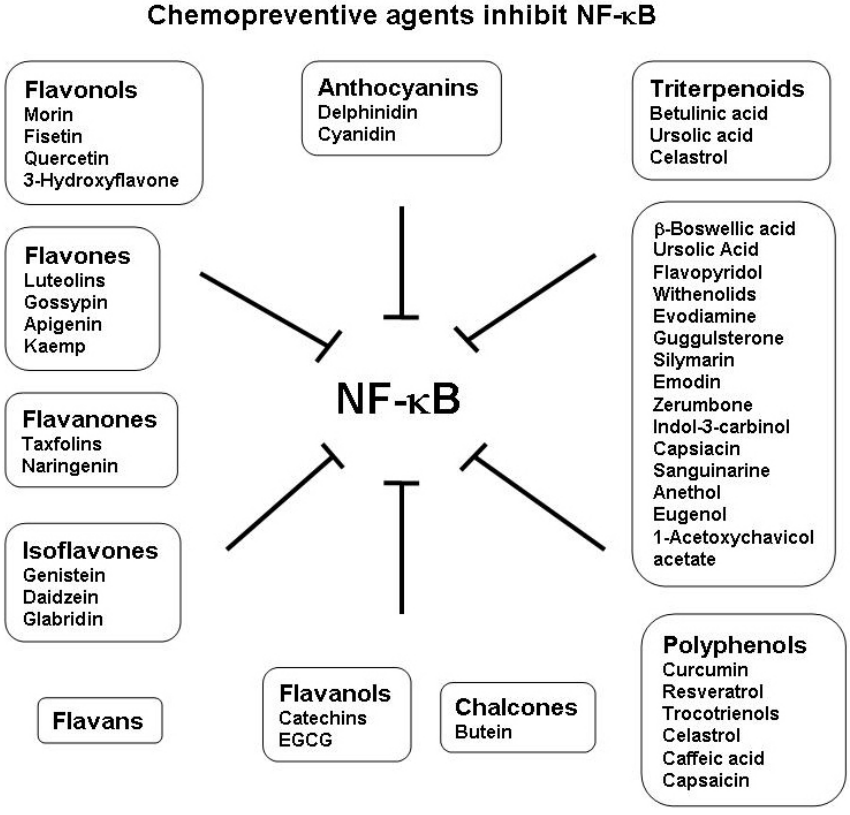

Figure 3. Chemopreventive agents inhibit NF-κB.

Table 2. Natural agents known to exhibit chemopreventive effects in animals

Curcumin (45,47)
Inhibits tumor promotion in mouse skin by TPA, UV-B light, BPDE
Inhibits azoxymethane-induced aberrant crypt foci formation in the rat colon
Inhibits forestomach, duodenal, and 1,2-dimethylhydrazine initiated colon carcinogenesis in Mice
Inhibits PhIP-induced tumour formation in Apc (min) mice
Prevents Familial Adenomatous Polyposis
Suppresses methyl (acetoxymethyl) nitrosamine, 4-nitroquinoline 1-oxide –induced hamster oral carcinogenesis
Inhibits benzo (a)pyrene-induced forestomach cancer in mice
Inhibits N-nitrosomethylbenzylamine-induced esophageal carcinogenesis in rats
Prevents N-methyl-N'-nitro-N-nitrosoguanidine and NaCl-induced glandular stomach carcinogenesis
Inhibits formation of DMBA, radiation-induced mammary tumors and lymphomas/leukemias in Sencar mice.
Prevents intravesical tumor growth of the MBT-2 tumor cell line following implantation in C3H mice
Resveratrol (45,48)
Inhibits DMBA-induced preneoplastic lesions in mouse skin cancer model
Inhibits UV-B exposed, DMBA-induced mouse mammary cell growth and TPA- promoted mouse skin tumor
Inhibits AOM-induced colon cancer in F344 rats, decreases number of ACF/ colon, their multiplicity and abolishes large ACFs
Inhibits estrogen–dependent preneoplastic ductal lesions induced by DMBA and MNU in mouse mammary glands, reduces N-methyl-N-nitrosourea-induced mammary carcinoma in rats
Induces DNA-oxidation products in plasma, the area of GST-placental form positive foci in liver and number of ACF in F344 rats
Induces DNA-oxidation products in plasma, the area of GST-placental form positive foci in liver and number of ACF in F344 rats
Inhibits the growth of murine transplantable liver cancer, H22.
Does not affect lung tumor multiplicity induced by Ba (P) and NNK in A/J mice
Abrogates BPDE-DNA adduct induction by BaP in lungs of Balb/c mice and prevents against BaP-induced CYP1A1 expression.
Suppresses N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in F344rats
Silymarin (49,50)
Inhibits DMBA-TPA-induced tumor in mammary glands
Inhibits DMBA-TPA, BPO, UVB-induced skin tumor in SENCAR mice
Inhibits OH-BBN-induced urinary bladder carcinogenesis in male ICR mice
Inhibits Azoxymethane-induced colon carcinogenesis in male F344 rats
Inhibits NQO-induced tongue carcinogenesis in male F344 rats
Indole 3-carbinol (51,52)
Inhibits 2-amino-1-methyl-6-phenylimidazo (4,5-b)pyridine (PhIP)-induced DNA adducts and colonic aberrant crypts in the F344 rat
Inhibits diethylnitrosamine-induced preneoplastic GST-P-positive liver cell foci in Sprague–Dawley rats
Inhibits polycyclic aromatic hydrocarbon-induced neoplasia
Inhibits mammary tumorigenesis in rats and mice
Inhibits diethylnitrosamine-induced hepatocarcinogenesis in male ACI/N rats and infant mouse
Inhibits colon tumour formation in mice
Deguelin (53)
Inhibits DMBA/TPA induced skin carcinogenesis with CD-1 mice and the N-methylnitrosourea
Inhibits DMBA/TPA induced skin carcinogenesis with CD-1 mice and the N-methylnitrosourea induced mammary carcinogenesis in Sprague Dawley rats, UVB-induced skin carcinogenesis
Suppresses the formation of carcinogen-induced aberrant crypt foci in the colon of CF-1 mice.
Inhibits benzo (a)pyrene-induced lung tumorigenesis in A/J mice, tobacco-induced lung tumorigenesis
Tocotrienols (55)
Inhibits diethylnitrosamine and 2-acetylaminofluorene-induced hepatocarcinogenesis in rats
Inhibits 7,12-dimethylbenz (a)anthracene (DMBA) induced tumor
Suppresses liver and lung carcinogenesis in mice.
Induces radiation sensitivity of prostate cancer in nude mice
Honokiol (56)
Inhibits TPA-induced skin tumor promotion in two stage carcinogenesis test in mouse
Inhibits angiosarcoma in nude mice.
Induces cytotoxicity in tumor cells from patients with relapsed refractory MM
Embelin (57)
Inhibits N-NDA/phenobarbital-induced hepatocarcinogenesis in Wistar rats
Indirubin (58)
Inhibits 2,4, 6-trinitro-l-chlorobenzene (TNCB)-induced ear swelling in mice.
Plumbagin (61)
Inhibits solid tumor (sarcoma-180) and Ehrlich ascites model in BALB/C mice
Inhibits azoxymethane-induced intestinal carcinogenesis in rats.
Effects radiation induced cytogenetic and cell cycle changes in mouse Ehrlich ascites carcinoma
Celastrol (63)
Suppresses human prostate cancer growth in nude mice
Inhibits systemic lupus erythematosus induced by active chromatin in BALB/c mice
Gossypin (64)
Inhibits development of carrageenin-induced paw oedema in mice
Capsaicin (66)
Suppresses tumor-induced angiogenesis in chick chorioallantoic membrane
Inhibits 7,12-dimethylbenz (alpha)anthracene induced skin carcinogenesis
Inhibits azoxymethane-induced rat colon carcinogenesis
Inhibits BP and DMBA induced mouse lung tumor formation
Inhibits prostate tumor in xenograft prostate tumor model
Boswellia (70)
Inhibits glioma growth
Inhibits TPA/DMBA induced skin carcinogenesis
Diosgenin (71)
Inhibits azoxymethane-induced aberrant crypt foci formation in F344 rats
Zerumbone (73)
Suppresses the initiation and promotion of skin tumors in mice
Prevents azoxymethane-induced aberrant crypt foci formation in rats
Suppresses dextran sodium sulfate-induced colitis in mice
Inhibits the activation of the phorbol ester-induced Epstein-Barr virus activation

Values in parentheses indicate the reference.

PPAR-γ, beta catenin, STAT3, and early growth response protein 1 (EGR1), leading to inhibition of the expression of COX-2, cyclin D1, adhesion molecules, MMP-9, iNOS, human epidermal growth factor receptor 2 (HER2), epithelial growth factor receptor (EGFR), bcl-2, bcl-xl, and TNF. Pharmacologically, curcumin is quite safe, and doses as high as 8 g/day have been administered orally to humans with no adverse effects.

5.2. Resveratrol

Resveratrol, *trans*-3,5,4'-trihydroxystibene, was first isolated in 1940 as a constituent of the root of white hellebore (*Veratrum grandiflorum O. Loes)*, but has since been found in various plants, including grapes, berries, and peanuts (47, 50). Besides cardioprotective effects, resveratrol exhibits anticancer properties as suggested by its ability to suppress proliferation of a wide variety of tumor cells, including lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid; melanoma; head and neck squamous cell carcinoma; ovarian carcinoma; and cervical carcinoma. The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; up-regulation of $p21^{Cip1/WAF1}$, p53, and Bax; down-regulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-x_L, and cIAPs; and activation of caspases. Resveratrol has been shown to suppress the activation of several transcription factors, including NF-κB, AP-1, and EGR-1; to inhibit protein kinases including inhibitor of NF-κB (IκBα) kinase (IKK), Jun N-terminal kinase (JNK), mitogen-activated protein kinase (MAPK), protein kinase B (Akt), protein kinase C (PKC), protein kinase D (PKD), and casein kinase II; and to down-regulate products of genes such as *COX-2, 5-LOX, VEGF, IL-1, IL-6, IL-8*, androgen receptor, and prostate-specific antigen (*PSA*)**.** These activities account for the suppression of angiogenesis by this stilbene.

Resveratrol also has been shown to potentiate the apoptotic effects of cytokines (e.g., TNF-related apoptosis-inducing ligand (TRAIL)), chemotherapeutic agents, and gamma-radiation. Pharmacokinetic studies revealed that the target organs of resveratrol are liver and kidney, where it is concentrated after absorption and is mainly converted to a sulfated form and a glucuronide conjugate. *In vivo*, resveratrol blocks the multistep process of arcinogenesis at various stages: it blocks carcinogen activation by inhibiting aryl hydrocarbon-induced CYP1A1 expression and activity and suppresses tumor initiation, promotion, and progression. Besides chemopreventive effects, resveratrol appears to exhibit therapeutic effects against cancer. Limited data in humans have revealed that resveratrol is pharmacologically quite safe. Currently, structural analogues of resveratrol with improved bioavailability are being pursued as potential therapeutic agents for cancer.

5.3. Silymarin

Silymarin comprises a family of flavonoids (silybin, isosilybin, silychristin, silydianin, and taxifoline) commonly found in the dried fruit of the milk thistle plant *Silybum marianum* (51, 52). Although silymarin's role as an antioxidant and hepatoprotective agent is well known, its role as an anticancer agent has begun to emerge. Extensive research within the last decade has shown that silymarin can suppress the proliferation of a variety of tumor cells (*e.g.,* prostate, breast, ovary, colon, lung, and bladder). It accomplishes this through cell cycle arrest at the G_1/S phase, induction of cyclin-dependent kinase (CDK) inhibitors (such as p15, p21 and p27), down-regulation of antiapoptotic gene products (*e.g.,* Bcl-2 and Bcl-xL), inhibition of cell-survival kinases (Akt, PKC, and MAPK), and inhibition of inflammatory transcription factors (*e.g.,* NF-κB). Silymarin also can down-regulate gene products involved in the proliferation of tumor cells (cyclin D1, EGFR, COX-2, transforming growth factor (TGF)-β, insulin-like growth factor receptor 1), invasion (MMP-9), angiogenesis (VEGF), and metastasis (adhesion molecules). The anti-inflammatory effects of silymarin are mediated through suppression of NF-κB–regulated gene products, including COX-2, LOX, iNOS, TNF, and IL-1. Numerous studies indicate that silymarin is a chemopreventive agent *in vivo* against a variety of carcinogens/tumor promoters, including ultraviolet light, 7,12-dimethylbenz (a)anthracene (DMBA), phorbol 12-myristate 13-acetate, and others (Table 2). Silymarin also has been shown to sensitize tumors to chemotherapeutic agents through down-regulation of the multidrug resistance protein and other mechanisms. It binds to both estrogen and androgen receptors and down-regulates PSA. In addition to its chemopreventive effects, silymarin exhibits antitumor activity against human tumors (*e.g.,* prostate and ovary) in rodents. Various clinical trials have indicated that silymarin is bioavailable and pharmacologically safe. Studies are now in progress to demonstrate the clinical efficacy of silymarin against various cancers.

5.4. Indole-3-carbinol

Indole-3-carbinol (I3C) is produced by members of the family Cruciferae, and particularly members of the genus *Brassica* (e.g., cabbage, radishes, cauliflower, broccoli, Brussels sprouts, and daikon) (53, 54). Under acidic conditions, I3C is converted to a series of oligomeric products (among which 3,3'-diindolylmethane is a major component) thought to be responsible for its biological effects *in vivo*. *In vitro*, I3C has been shown to suppress the proliferation of various tumor cells, including breast cancer, prostate cancer, endometrial cancer, colon cancer, and leukemia; induce G_1/S arrest of the cell cycle; and induce apoptosis. The cell cycle arrest involves down-regulation of cyclin D1, cyclin E, CDK2, CDK4, and CDK6 and up-regulation of p15, p21, and p27. Apoptosis by I3C involves down-regulation of antiapoptotic gene products, including bcl-2, bcl-xl, survivin, IAP, XIAP, and cFLIP; up-regulation of proapoptotic protein bax; release of mitochondrial cytochrome C; and activation of caspase-9 and caspase-3. This agent inhibits the activation of various transcription factors including NF-κB, SP-1, estrogen receptor, androgen receptor, and NRF2. This indole potentiates the effects of TRAIL through induction of death receptors, and synergizes with chemotherapeutic agents through down-regulation of P-glycoprotein. *In vivo*, I3C was found to be a potent chemopreventive agent for hormone-dependent cancers such as those of the breast and cervix. These effects are mediated through its ability to induce apoptosis, inhibit DNA-carcinogen adduct

formation, suppress free-radical production, stimulate 2-hydroxylation of estradiol, and inhibit invasion and angiogenesis. Numerous studies have indicated that I3C also has a strong hepatoprotective activity against various carcinogens.

5.5. Deguelin

Deguelin is a rotenoid from the African plant *Mundulea sericea* (Leguminosae), which was identified as a potent chemopreventive agent on the basis of its action against chemically induced preneoplastic lesions in a mammary organ culture and its inhibition of papillomas in a two-stage mouse skin carcinogenesis model (55). Deguelin also has been found to suppress the formation of carcinogen-induced aberrant crypt foci in mouse colons**.** More recently, this rotenoid was shown to suppress cigarette smoke–induced lung carcinogenesis. Deguelin has been shown to enhance the sensitivity of leukemia cells to chemotherapeutic agents. How deguelin mediates its chemopreventive and chemosensitizing effects is not yet fully understood, but various mechanisms have been proposed, including suppression of ornithine decarboxylase, inhibition of the phosphatidylinositol 3-kinase/Akt pathway, and down-regulation of COX-2 and cyclin D1. We showed that deguelin mediates several of its effects through modulation of the NF-κB pathway (55).

5.6. Tocotrienols

While both tocopherols and tocotrienols exist as alpha, beta, gamma, and delta forms and are members of the vitamin E family, the two differ structurally in that tocopherols contain a saturated phytyl chain, whereas tocotrienols possess an unsaturated side chain. The sources of these vitamins also differ: tocopherols are components of nuts and common vegetable oils, whereas tocotrienols are derived primarily from oat, wheat germ, barley, rye, rice bran, and palm oil (55). The unsaturated side chain present in tocotrienols facilitates its entry through the membrane bilayer more efficiently than the saturated chain of tocopherol. In spite of this advantage and some reports that tocotrienols are better antioxidants, there are 11,900 Pubmed citations on tocopherol and fewer than 300 on tocotrienols. There are reports suggesting that tocotrienols may have, besides their activity again atherosclerosis, potential against cancer. For instance, tocotrienols have been shown to suppress the proliferation of a wide variety of tumor cells in culture, including breast, prostate, and colon. Animal studies have shown that tocotrienols can suppress the growth of breast tumors and melanoma and inhibit liver and lung carcinogenesis. Tocotrienols possess powerful neuroprotective, anticancer, and cholesterol-lowering properties that are often not exhibited by tocopherols. When mammary tumors were induced by DMBA, only mice given tocotrienol had a significant increase in tumor latency; tocopherol had no effect. Similarly, only tocotrienol, not tocopherol, blocked stress-induced changes in gastric acidity and gastrin level. Moreover, in contrast to tocotrienol, tocopherol showed very weak telomerase inhibition. A recent study has shown the ability of tocotrienols to preferentially sensitize prostate cancer to gamma-radiation in nude mice.

How tocotrienols mediate their effects is not fully understood, but their abilities to induce cell cycle arrest, regulate HMG-COA reductase, activate p53, activate caspase-8, suppress adhesion molecules, down-regulate c-myc and telomerase, and inhibit angiogenesis have been established. Because of the critical role of the NF-κB pathway in tumorigenesis, radiosensitization, apoptosis, cell adhesion, expression of c-myc and human telomerase reverse transcriptase, and cell cycle arrest, we postulated that γ-tocotrienol must modulate this pathway. We demonstrated that γ-tocotrienol can suppress NF-κB activated by inflammatory cytokines, growth factors, and tumor promoters through inhibition of IKK, leading to suppression of NF-κB–regulated gene products and potentiation of apoptosis (55).

5.7. Honokiol

Honokiol, used for almost three decades as a muscle relaxant, is derived from the stem and bark of the plant *Magnolia officinalis,* which is used in traditional Chinese and Japanese medicine (56). Extensive research has shown that honokiol inhibits skin tumor promotion, inhibits nitric oxide synthesis and TNF expression, inhibits invasion, down-regulates antiapoptotic protein bcl-xl, inhibits angiogenesis and tumor growth *in vivo*, induces caspase-dependent apoptosis in B-cell chronic lymphocytic leukemia cells through down-regulation of the antiapoptotic protein Mcl-1, and overcomes drug resistance in multiple myeloma. Exactly how honokiol mediates all these effects is poorly understood. We have shown that honokiol is a potent inhibitor of NF-κB activation and NF-κB-regulated carcinogenic gene products (56).

5.8. Embelin

The fruit of the *Embelia ribes Burm.* plant (Myrsinaceae--called false black pepper in English, Vidanda in Sanskrit, and Babrang in Hindi languages) has been used to treat fever, inflammatory diseases, and a variety of gastrointestinal ailments for thousands of years (59). More than four decades ago, the active component from this plant was isolated and named embelin; later it was chemically synthesized. Embelin has been shown to have antitumor, anti-inflammatory, and analgesic properties, and it has been shown to decrease testosterone levels, induce apoptosis in human myeloid HL-60 cells by targeting microtubular proteins, induce cleavage of receptor-interacting protein through activation of caspases during pancreatitis, and inhibit *N*- /Phenobarbital–induced hepatocarcinogenesis in Wistar rats. More recently, embelin was identified as a cell-permeable, small-molecular-weight inhibitor of XIAP, an antiapoptotic protein, through structure-based computational screening of a three-dimensional structure database of 8,221 individual traditional herbal products. We recently showed that embelin can suppress the NF-κB signaling pathway, leading to suppression of NF-κB–regulated antiapoptotic and metastatic gene products (57).

5.9. Indirubin

Indirubin is the purple component of blue indigo dye, extracted from plants such as *Polygonum tinctorium,*

Isatis indigotica, and *Isatis tinctoria*. Chemically, indirubin is a 3, 2'-bisindole, a stable isomer of indol dimmers (58). It has been shown to inhibit cell growth and induce apoptosis and differentiation of leukemic cells. Indirubin and its derivatives bind to and inhibit CDK1/cyclin B, CDK2/cyclin A, CDK2/cyclin E, and CDK5/p25, displaying potent growth-inhibitory effects in various human tumors. Moreover, indirubin derivatives bind to and inhibit glycogen synthase kinase-3β, c-src kinase, aryl hydrocarbon receptor, and rabbit muscle glycogen phosphorylase b. Indirubin was shown recently to inhibit c-Jun NH2-terminal kinase. The molecule has anti-inflammatory effects, as indicated by its ability to inhibit 2,4,6-trinitro-1-chlorobenzene–induced inflammatory reactions in mice, and suppresses expression of the influenza virus-induced chemokine RANTES in human bronchial epithelial cells, suggesting that it may suppress the NF-κB activation pathway. We showed that indirubin can potentiate apoptosis and down-regulates invasion through inhibition of NF-κB–regulated antiapoptotic and metastatic gene expression (58).

5.10. Plumbagin

Plumbagin is a naturally occurring yellow pigment found in the plants of the Plumbaginesea, Droseracea, Ancestrocladaceae, and Dioncophyllaceae families. The root of *Plumbago zeylanica* (also called Chitrak), a major source of plumbagin, has been used in Indian medicine since the period of Charaka (from 750 BC) as an antiatherogenic, cardiotonic, hepatoprotective, and neuroprotective agent (59, 60). The active principle, plumbagin, was first isolated in 1829. Plumbagin is also present along with a series of other structurally related naphthoquinones in the roots, leaves, bark, and wood of *Juglans regia* (English walnut, Persian walnut, California walnut), *Juglans cinerea* (butternut and white walnut), and *Juglans nigra* (black walnut). Preparations derived from black walnut have been used as hair dyes and skin colorants in addition to being applied topically for the treatment of acne, inflammatory diseases, ringworm, and fungal, bacterial, and viral infections.

Plumbagin has been shown to exert anticancer and antiproliferative activities in animal models as well as in cells in culture. This quinone has been shown to significantly inhibit azoxymethane-induced intestinal carcinogenesis in rats, suggesting its chemopreventive activity. Plumbagin also has been shown to induce S-G_2/M cell cycle arrest through induction of p21 (an inhibitor of CDK). A recent report showed that plumbagin has chemotherapeutic potential as an anticancer agent in ovarian cancer cells with a mutated *BRCA1* gene. The cytotoxic action of plumbagin in keratinocytes and cervical cancer cells was found to be due to change in the redox status of the cell. In embryonic kidney and brain tumor cells, plumbagin inhibited the enzyme NAD (P)H oxidase, an effect linked with anticarcinogenic and atherosclerotic effects. Besides anticancer effects, plumbagin also exhibited radiosensitizing properties in experimental mouse tumors as well as in tumor cells *in vitro*. We showed that plumbagin can suppress NF-κB activation and NF-κB–regulated gene products, leading to potentiation of apoptosis induced by cytokines and chemotherapeutic agents (61).

5.11. Celastrol

Also known as tripterine, celastrol was originally identified from a traditional Chinese medicine (God of Thunder vine) almost three decades ago and is used for the treatment of cancer and other inflammatory diseases (62). A triterpenoid from the Celastracae family, extracted from the plant *Tripterygium wilfordii*, celastrol has attracted interest, especially for its potential anti-inflammatory effects, which have been demonstrated *in vivo* in animal models of collagen-induced arthritis, Alzheimer's disease, asthma, systemic lupus erythematosus, and rheumatoid arthritis. Celastrol is also known to inhibit proliferation of a variety of tumor cells, including those from leukemia, gliomas, and prostate cancer. Celastrol's abilities to modulate the expression of proinflammatory cytokines, major histocompatibility complex II antigen, iNOS, adhesion molecules in endothelial cells, proteasome activity, topoisomerase II, potassium channels, and heat shock response have been reported **.** The molecular mechanism underlying the anti-inflammatory and antiproliferative effects of celastrol is not yet fully understood. We have demonstrated that celastrol can potentiate TNF-induced apoptosis and suppresses invasion of tumor cells by inhibiting NF-κB–regulated gene products and NF-κB activation (63).

5.12. Gossypin

Gossypin, a glucosyl flavone, was originally isolated from *Hibiscus vitifolius* (tropical rose mallow, also called *Japa* or *Karupatti*); and *H. furcatus* (also called *Panchavam* in Malayalam). The extracts of these plants are traditionally used for treatment of diabetes, jaundice, and inflammation. The very limited information available on this flavone indicates that it exhibits potent antioxidant activity, suppresses amyloid-induced toxicity, mediates antinociception by modulating the gamma amino butyric acid system, protects against carbon tetrachloride–induced toxicity in rat hepatocytes, and protects against *bis* (2-choloroethyl)sulfide–induced dermal toxicity. Gossypin also has anti-inflammatory activity; it prevented carrageenan-induced paw edema in mice by inhibiting arachidonic acid metabolism. Gossypin has been found to inhibit cell proliferation in L929, HT29, and K562 tumor cell lines in culture. In mice, it inhibited the growth of Ehrlich's ascites carcinoma and inhibited angiogenesis. It also exhibited anticarcinogenic activity against DMBA/croton oil–induced papilloma in rodents. Gossypin's antitumoral effects have been ascribed partly to its ability to inhibit topoisomerase I and II. However, the exact mechanisms of its anti-inflammatory and anticarcinogenic properties are not fully understood. We showed that gossypin inhibits the NF-κB activation pathway, leading to potentiation of apoptosis, suppression of invasion, and abrogation of osteoclastogenesis (64).

5.13. Capsaicin

Capsaicin is a principal pungent ingredient of hot red and chili peppers that belong to the plant genus *Capsicum (*Solanaceae). In addition to alleviating

neuropathic pain and itching in humans, capsaicin has exhibited anticancer effects in animal models, suppressing carcinogenesis of the skin, colon, lung, tongue, and prostate. The mechanism by which this vanilloid mediates its anticarcinogenic effects is not understood, but it has been shown to alter the metabolism of carcinogens such as aflatoxin B1 and the tobacco-specific nitrosamine 4-(methylnitrosamino)-1- (3-pyridyl)-1-butanone. In culture, capsaicin has been found to selectively suppress the growth of various human tumor cells including leukemia, glioma, and cancers of the stomach, liver, and prostate. The roles of NADH oxidase activity, proteasome, cyclo-oxygenases, JNK, PPAR-γ, peroxynitrite, and mitochondrial respiration have been linked to the anticancer effects of capsaicin. We showed that capsaicin can suppress both NF-κB (65) and STAT-3 (66) activation pathways. Its immunosuppressive effects have been linked to its ability to suppress NF-κB activation.

5.14. Withanolids

Withania somnifera Dunal is one of the most ancient and sought-after herbs (also called Winter Cherry) for the preparation of herbal formulations and dietary supplements. It belongs to the family Solanaceae and is distributed throughout India. In traditional Indian medicine, or Ayurveda, the leaves and roots were prescribed to cure inflammation-related disorders. This plant has been studied extensively for its biologically active constituents and has yielded several steroidal lactones called withanolides. A pharmacological study conducted on this plant indicated that a component withanolide, withaferin A, inhibits angiogenesis. Withanolides have also been reported to inhibit metastasis and quinone reductase activity. Some of them have been shown to preferentially affect events in the cholinergic signal transduction cascade of the cortical and basal forebrain, indicating their promise for the treatment of Alzheimer's disease. Despite these findings of withanolide pharmacological activity, their mechanisms of action remain unknown. We and others have shown that withanolide can inhibit the NF-κB pathway, leading to potentiation of apoptosis; inhibit invasion; and abolish osteoclastogenesis (67, 68).

5.15. Guggulsterone

Guggulsterone is a plant sterol derived from the gum resin (guggulu) of the tree *Commiphora mukul*. The resin has been used in Ayurvedic medicine for centuries to treat a variety of ailments, including obesity, bone fractures, arthritis, inflammation, cardiovascular disease, and lipid disorders. The antiarthritic and anti-inflammatory activity of gum guggul was demonstrated as early as 1960, followed by a report of activity in experimental arthritis induced by mycobacterial adjuvant and another on the effectiveness of guggul for treating osteoarthritis of the knee. Recent studies have shown that guggulsterone is an antagonist for the bile acid receptor farnesoid X receptor. Other studies have shown that guggulsterone enhances transcription of the bile salt export pump, thereby regulating cholesterol homeostasis. We reported that guggulsterone suppressed the DNA binding of NF-κB induced by various carcinogens and inflammatory agents (69).

5.16. Boswellia

The gum resin of the plant *Boswellia serrata (*also known as *Salai guggul*) is used in the Ayurvedic system of medicine for the treatment of rheumatic diseases, respiratory diseases, and liver disorders. Extensive research within the last 30 years has identified the active component of this resin as boswellic acid (BA, a pentacyclic triterpenic acid) and its derivatives (acetyl-β-boswellic acid, 11-keto-β-boswellic acid, and acetyl-11-keto-β-boswellic acid, or AKBA). The traditional therapeutic usefulness of BA is the result of its anti-inflammatory activity, possibly mediated through inhibition of 5-LOX and leukocyte elastase. In experimental animal models of inflammation, BA has been shown to be effective against Crohn's disease, ulcerative colitis, and ileitis, adjuvant or bovine serum albumin–induced arthritis, galactosamine/endotoxin-induced hepatitis in mice, and osteoarthritis. Besides its anti-inflammatory effects, BA also exhibits antitumor effects as indicated by its activity against brain tumors cells**,** leukemic cells, colon cancer cells, metastatic melanoma and fibrosarcoma cells, and hepatoma cells. BA also has been shown to inhibit azoxymethane-induced formation of aberrant crypt foci in the colon of mice.

How BA mediates its many effects is poorly understood. It has been shown to induce cell cycle arrest; suppress MMP activity; down-regulate the expression of cyclinD1, Bcl-2, and Bcl-x_L; and induce apoptosis. BA inhibits lipopolysaccharide-mediated production of TNF, one of the most potent inducers of apoptosis and inflammation. Most of the proinflammatory effects of TNF are mediated through activation of NF-κB. This transcription factor also has been shown to suppress apoptosis induced by TNF and chemotherapeutic agents. Whether AKBA modulates TNF signaling is not understood. RANKL, another member of the TNF superfamily, has been found to mediate osteoclastogenesis through the NF-κB activation pathway. The results showed that AKBA potentiated apoptosis induced by TNF and chemotherapeutic agents, inhibited TNF-induced cell invasion, and abrogated RANKL-induced osteoclastogenesis through inhibition of NF-κB activation (70).

5.17. Diosgenin

Diosgenin is a steroidal saponin found in a variety of plants, including fenugreek (*Trigonella foenum graecum*), roots of wild yam (*Dioscorea villosa*), *Solanum incanum* Lloydia, *Costus speciosus*, and *Solanum xanthocarpum*. Extracts from these plants have been used traditionally for the treatment of diabetes, hypercholesterolemia, and gastrointestinal ailments. Research during the last decade has shown that diosgenin suppresses proliferation and induces apoptosis in cells of human colon carcinoma, osteosarcoma, leukemia, human erythroleukemia, and human rheumatoid arthritis. Antiproliferative effects of diosgenin are mediated through cell cycle arrest, disruption of calcium homeostasis, activation of p53, release of apoptosis-inducing factor, and modulation of

caspase-3 activity. It inhibits azoxymethane-induced aberrant colon crypt foci and has been shown to inhibit intestinal inflammation and modulate the activity of lipoxygenase and COX-2. More recently, diosgenin has been shown to bind to the chemokine receptor CXCR3, which mediates inflammatory responses. We found that diosgenin inhibited TNF-induced invasion of tumor cells and osteoclastogenesis induced by RANKL through the inhibition of NF-κB and NF-κB–regulated gene products (71). Diosgenin also potentiated the apoptosis induced by TNF and the chemotherapeutic drugs doxorubicin and paclitaxel (71).

5.18. Zerumbone

This polyphenol was first isolated in 1956 from the essential oil of rhizomes of a wild ginger, *Zingiber zerumbet* Smith, which is widespread in Southeast Asia. Over the years, a wide variety of activities have been assigned to this compound. For instance, zerumbone has been found to suppress the proliferation of colon cancer and breast cancer, with minimal effects on normal cells. Zerumbone has been shown to suppress inflammation, suppress the initiation and promotion of skin tumors in mice, and prevent azoxymethane-induced aberrant crypt foci formation in rats. This terpenoid has also been shown to suppress dextran sodium sulfate–induced colitis in mice (72) and to inhibit activation of the phorbol ester-induced Epstein-Barr virus. Additional activities attributed to zerumbone are suppression of superoxide and nitric oxide generation and down-regulation of COX-2, IL-1β, and TNF. Several of these activities could be explained if zerumbone down-regulates NF-κB activation, since zerumbone has proven effects on related activities.

We hypothesized that zerumbone interferes with the NF-κB activation pathway and suppresses gene transcription. We tested this hypothesis by determining the effect of zerumbone on NF-κB and NF-κB–related gene expression activated by various inflammatory agents (73). Our results showed that zerumbone can indeed suppress the NF-κB activation induced by a wide variety of agents, irrespective of cell type; it suppresses the expression of various antiapoptotic and proliferative gene products, enhances apoptosis, and suppresses carcinogenesis induced by cytokines and chemotherapeutic agents.

5.19. Evodiamine

The fruit of "Wu-Zhu-Yu" (*Evodiae Fructus; Evodia rutaecarpa* Benth., Rutaceae) is used in traditional Chinese medicine as a cardiotonic. The active constituents of this fruit are evodiamine and rutaecarpine, which are indole alkaloids found in large amounts in the Chinese medicine evodia and are the main compounds responsible for the medicine's antianoxic action. Evodiamine has been shown to suppress proliferation of a wide variety of tumor cells, including prostate and cervical cancer cells, leukemic T lymphocytes, monocytic leukemia cells, melanoma cells, and mouse fibrosarcoma cells, but it apparently has no toxic effects against normal peripheral blood mononuclear cells. Evodiamine induces apoptosis in tumor cells by up-regulating Bax, down-regulating Bcl-2, phosphorylating Bcl-2, activating caspases, and producing nitric oxide. Besides its antiproliferative and apoptotic effects, evodiamine suppresses the invasion and migration of human colon carcinoma cells and melanoma cells to the lung. We showed that this compound mediates its effects by modulating the NF-κB activation induced by a wide variety of agents, irrespective of cell type, suppressed expression of various antiapoptotic and proliferative gene products, and enhanced the apoptosis and suppressed the invasive activity induced by cytokines and chemotherapeutic agents (74).

5.20. Catechins

Green tea (*Camellia sinensis*) is one of the most widely consumed beverages worldwide. Dried tea extract contains 25% to 40% polyphenols, including flavonols (catechins), of which epigallocatechin gallate (EGCG) is the most prevalent and extensively studied. Green tea phenols have many biological activities that include antioxidative properties, inhibition of cell growth, and antiviral and antiproliferation activities. Anticarcinogenic effects of EGCG and other green tea phenols on various organs such as skin, stomach, duodenum, colon, liver, pancreas, and lung in rodent models have been confirmed to be mediated through arrest of the cell cycle and induction of apoptosis. A well-conducted case-control study in Shanghi, China, demonstrated that consumption of green tea reduces the risk of esophageal cancer among women. Injections of EGCG have been shown to reduce the size of human prostate and breast tumors in nude mice. EGCG was also found to strongly and directly inhibit telomerase, an enzyme essential for unlocking the proliferative capacity of cancer cells by maintaining the tips of their chromosomes. These studies have suggested several possible mechanisms of action of green tea and its components. These include antioxdant properties, interaction with certain enzymes or proteins implicated in cancer biology such as urokinase, ornithine decarboxyase, NADPH-cytochrome P450 reductase, PKC, steroid 5 alpha reductase, TNF, and nitric oxide synthase.

Many of the these mechanisms require down-regulation of NF-κB activation, as EGCG inhibits lipopolysaccharide-induced expression of the *TNF-α* gene, production of nitric oxide, and expression of the *iNOS* gene in macrophages via blocking of NF-κB activation. Furthermore, EGCG down-modulates the constitutive NF-κB in the cytoplasm and nucleus of human epidermoid carcinoma cells. Pianetti *et al.* showed EGCG inhibits Her-2/neu signaling by down-regulating NF-κB via the PI3/AKT kinase signaling pathway (75). Yang *et al.* have shown that EGCG inhibits NF-κB activation in TNF-α–treated intestinal cells by blocking phosphorylation of IkB alpha, that the gallate group with catechin backbone is essential for this inhibition, and that gallic acid methyl esters are very weak inhibitors in cell free systems while the catechin backbone confers greater efficacy (76). Polyphenols and antioxidants lacking the gallate group didn't inhibit IKK phosphorylation. Further, the presence of an extra hydroxyl group in EGCG may accentuate its inhibitory activity. Therefore, a combination of the gallate group, the catechin backbone, and an additional hydroxyl group in the structure of EGCG, (and other polyphenols) increases its efficacy and plays a crucial role in inhibiting NF-κB activation.

6. CLINICAL TRIALS OF CHEMOPREVENTIVE AGENTS

The molecular targets that can be employed are the same for cancer prevention and treatment (77, 78). Estrogen antagonist tamoxifen, for example, which was initially developed for cancer therapy, is now used for cancer prevention. Similarly, celecoxib, a COX-2 inhibitor approved for prevention of familial adenomatous polyposis, is now being considered for therapy of cancer. EGFR inhibitors that are approved for cancer therapy are now being explored for prevention. The basic requirements for any chemopreventive agent, besides efficacy, are affordability and safety, as they require administration over a long period of time. As shown in this review, numerous agents have been tested, but none have yet shown any clear efficacy.

7. CONCLUSION

Cancer is potentially the most preventable of the major life-threatening illnesses. Tobacco use, dietary factors, physical inactivity, and infections are major risk factors and account for many cases of cancer. While tobacco accounts for 22% of overall cancer burden, dietary factors are responsible for 30% (79). All of these risk factors appear to induce chronic inflammation through activation of NF-κB, which in turn links them to cancer. Because flavonoids, anthocyanins, flavones, terpenoids, catechins, and other polyphenols identified in fruits, vegetables, spices, and traditional medicines suppress NF-κB activation, they are likely to both prevent and treat cancer. More clinical trials in healthy individuals and those with cancer are needed to prove this point.

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Send correspondence to: Bharat B. Aggarwal, Cytokine Research Laboratory, Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Box 143, Houston, TX 77030 USA, Tel: 713-792-3503/6459, Fax: 713-794-1613, E-mail: aggarwal@mdanderson.org

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